REMARKS

The present invention relates to the use of $VPAC_2$ receptor agonists in the treatment of skeletal muscle atrophy or to induce skeletal muscle hypertrophy.

Claims 16, and 17 are pending in the application and are currently amended. Claims 1-14, 18-26, and 28 have been withdrawn. Claims 15, and 27 have been cancelled. Applicants respond in accordance to the Office Action of March 24, 2003.

1. Applicants respond to the Office Action's rejection of claims 15-17 and 27 under 35 U.S.C. §112, first paragraph (enablement). The Office Action restates Applicants' position in paragraphs 4A and 4B, and concludes by stating, "Applicants' argument in the last paragraph regarding VIP, PAPAC-27, PVI, GHRH etc. is in fact supporting the enablement rejection." Applicants cancel Claims 15, and 27 and request that any rejections directed to these claims be withdrawn.

   The Office Action rejects Claim 17 as including VIP, PACAP-27, PVI, GHRH, helodermin etc., in a Markush group of selective VPAC agonists. In response, Applicants amend Claims 16, and 17 to clarify that the agonists so claimed are selective for $VPAC_2$ receptor (as opposed to VPAC receptors generally). Basis for this amendment is found *inter alia* at page 8 line 13, and again at page 15 lines 31-32. Moreover, Applicants amend Claim 17 such that Markush group of selective $VPAC_2$ receptor agonists is limited to RO 25-1553 and PACAP-38. To this end, Applicants point out the following:

   a. Compound RO 25-1553 employed by Applicants in the specific embodiments is a highly specific $VAPC_2$ receptor specific agonist (see description of the figures, page 8, line 8; and article by Gourlet et al, *Peptides* (1997) 18(3), 403-8; included in the supplemental IDS).

   b. Applicants have used RO 25-1553 in their experiments. Specifically, results from these experiments (Figures 1A, 1B, 2A, and Figures 3-5) show that RO 25-1553 reduces skeletal muscle atrophy induced by various atrophy models in at least three different muscles examined. Results also show that RO 25-1553 induces hypertrophy in normal skeletal muscle (Figures 2A, 2B, and 4B). Thus, Applicants submit that these experiments employing RO 25-1553 demonstrate that $VPAC_2$ receptor-specific agonists

are effective in reversing the skeletal muscle atrophy and induce hypertrophy in normal muscle.

c. Applicants also want to draw attention to the fact that $VPAC_1$ (as opposed to $VPAC_2$) receptor specific agonists used in the study, namely K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2, do not show either atrophy-reducing or hypertrophy-inducing effects (see Figures 1-5). Positive effects seen in Figures 1B (bar 'C' at 0.3 mg/kg), 2B (bar 'D' at 3 mg/kg), and 3A (bar 'D' at 0.1 mg/kg), may be explained by higher amounts of $VPAC_1$ agonists used that may have some binding to $VPAC_2$ receptors. Also, it should be noted that these effects were neither consistently observed, nor were they observed in any dose-dependent manner. Similarly, positive effects seen with non-specific agonist PACAP-38, are explained by the fact that PACAP-38 binds $VPAC_2$ receptors. It is possible that unusually high local concentrations of an agonist that is not $VPAC_2$ receptor-specific may nevertheless lead to $VPAC_2$ receptor activation. In order to rule out that possibility, Applicants used an osmotic minipump to administer an agonist continuously, to achieve sustained, uniform, biologically available dose of the agonist. Data from Figure 2A and 2B show that $VPAC_2$ receptor selective agonist RO 25-1553, and not a $VPAC_1$ receptor agonist, is able to both induce hypertrophy and reduce atrophy of skeletal muscle.

d. It is well established in the art that both pancreas and skeletal muscle tissues express $VPAC_2$ receptors but they do not express either $VPAC_1$ or PACAP-Type 1 receptors as determined by RNase protection assay (See e.g., Wei et al, Journal of *Neuroendocrinology* (1996) 8, 811-817; Adamou et al, *Biochem. Biophys. Res. Commun.* (1995) 209, 385-392; both included in the supplemental IDS attached herein). Thus, the atrophy-reducing and hypertrophy-inducing effects seen in skeletal muscle tissues, of agonists that may not be specific for $VPAC_2$ receptor, but nevertheless bind the receptor, (for example, PACAP-38, which in addition to $VPAC_2$, also binds $VPAC_1$ and PACAP-type 1 receptors), are due to their binding to $VPAC_2$ receptor since muscle tissue expresses $VPAC_2$ receptors and not $VPAC_1$ or PACAP-type 1 receptors.

2. In points 5) and 6), the Office Action maintains the rejection of Claims 16, 17, and 27 under 35 U.S.C. §102(b) over Vittone (Vittone et al., *Metabolism*, 46, 89-96 (1997)). In support of rejecting Claims 16-17, the Office Action points out that Applicants do not claim doses of GHRH that would make it selective for VPAC receptors, and claim 17 lists GHRH as a selective VPAC agonist. Although the Examiner also rejects Claims 15 and 27 under 35

U.S.C. section 102(b), Applicants have canceled these claims, and therefore respectfully submit that any rejections directed to these claims should be withdrawn.

a. To overcome the rejection, Applicants have amended claims 16, and 17, such that only $\underline{VPAC_2}$ (as opposed to $VPAC_1$ or VPAC generally) receptor specific agonists are claimed.

b. As Applicants have pointed out earlier, skeletal muscle tissues express only $VPAC_2$ receptors and therefore limiting the claims to $VPAC_2$ receptor specific agonists overcomes the rejection in view of Vittone which is directed to a $\underline{non}$ specific $VPAC_2$ receptor agonists.

c. Cancellation of claim 15 leaves no composition claims in the present application and therefore removes 35 U.S.C. §102(b) rejection over Gourlet et al. Although Examiner's rejection is moot since Applicants canceled Claim 15, Applicants use the opportunity to point out that Gourlet et al. teaches the use of peptides that are selective for VIP_1 receptor as a therapeutic agent in the treatment of bronchoconstrictive disorders, of tumors, and of myocardial infarctions and strokes; while the present invention teaches use of peptides that are selective for $VPAC_2$ receptors in order to increase skeletal muscle mass or function. Gourlet et al never contemplate use of $VPAC_2$ receptor-specific agonists for treating muscle mass or function-related disorders.

3. The Office Action rejects Claims 15-17 and 27 under 35 U.S.C. §112, first paragraph, because the specification while being enabling for specific VPAC receptor agonists specific for either $VPAC_1$ ([K^{15}, R^{16}, L^{27}, VIP(1-7), GRF(8-27)-NH_2], $VPAC_2$ (RO 25-1553) or both $VPAC_1$ and $VPAC_2$ receptors (PACAP-38, pituitary adenylate cyclase-activating polypeptide), does not reasonably provide enablement for any other compound or any of the other ligands listed in claim 17.

a. Applicants point out that claims 15 and 27 are canceled and therefore any rejections to these claims are rendered moot.

b. Applicants again point out that claim 17 is amended to the specific $VPAC_2$ receptor agonists, RO 25-1553 and PACAP-38.

c. Applicants submit that the specification provides sufficient enablement to support amended Claims 16 and 17. To be enabling under 35 U.S.C. § 112, 1^{st} paragraph, a patent must contain a description that enables one skilled in the art to make and use the

claimed invention without "undue experimentation."[1] That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive.[2] To this end, courts have nearly axiomatically viewed enablement through the lens of "undue experimentation."[3] Factors to be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.[4] Applicants submit the requirements as detailed by *In re WANDS* are met as discussed below.

i. Applicants provide sufficient detailed description in the specification to make and use the invention. Identifying agonists that are specific for $VPAC_2$ receptor requires routine experimentation and expertise that are within the skills of an artisan conversant in the field of muscle biology. As exemplified by articles of Gourlet et al., (Peptides (1997) 18(3), 403-8; Peptides (1997) 18(10), 1539-1545, both included in the suppl. IDS); and patent application by Gourlet et al., (WO 98/02435, cited by the Examiner); it requires routine experimentation to design and identify compounds that are selectively specific for $VPAC_1$ or $VPAC_2$ receptors. Applicants therefore used agonists that are specific to each VPAC receptor and also used an agonist that is not, to show the specificity of response exhibited by $VPAC_2$ receptor agonist. Thus, Applicants believe that no undue experimentation is required to practice the invention.

ii. Applicants emphasize that the specification teaches one skilled in the art how to use $VPAC_2$ receptor agonists to treat skeletal muscle atrophy. A $VPAC_2$ receptor-specific agonist may be used in the treatment of muscle atrophy or to achieve muscle hypertrophy. The specification provides means of identifying

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[1] *Genetech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365 (Fed. Cir. 1997). For a disclosure to be enabling, enough reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1374 (Fed. Cir. 1999)

[2] *Atlas Powder Co. v. E.I. duPont De Nemours & Co.*, 750 F.2d 1569,1576 (Fed. Cir. 1984). "The essential question here is whether the scope of enablement of is as broad as the scope of the claim." *Amgen, Inc. v. Chugai Pharaceutical Co.*, 927 F.2d 1200, 1211 (Fed. Cir. 1991).

[3] See, e.g., *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (C.C.P.A. 1976);*In re Forman*, 230 U.S.P.Q. 546,547 (Bd. Pat. App. & Int/ 1986); *In re Wands*, 858 F.2d 731, 737-38 (Fed. Cir. 1988).

[4] *In re WANDS*, 858 F.2d 731, 737 (Fed. Cir. 1988) citing *In re Forman*, 230 U.S.P.Q. 546,547 (Bd. Pat. App. & Int/ 1986).

compounds as $VPAC_2$ receptor agonists using cell-free and cell-based assay systems (pages 23-30, Sections V and VI). It further provides cell-based or animal models of muscle atrophy that may be used to further validate these agonists (pages 30-30-34, Section VII) in the treatment for increasing skeletal muscle mass or function. Finally, the specification provides pharmacological formulations, dose determinations, uses of these agonists, and means of monitoring effects of the agonists during clinical trials (pages 35-37, Section IX). Thus, ample directions and guidance are provided in the specification for a skilled artisan to successfully practice the invention.

iii. Applicants provide examples how to practice the invention as described (Examples 1-11). Further, Figures 1-5 show examples of treatment of mice and rats with agonists of VPAC receptors. In these examples, Applicants describe embodiments using various muscle atrophy models like denervation-induced muscle atrophy, glucocorticoid-induced muscle atrophy, and casting (disuse)-induced muscle atrophy; various muscles like tibialis anterior, medial gestrocnemius, and extensor digitorum longus (EDL) muscles, various means of administration of agonists, various animal species, and different VPAC receptor agonists. Therefore, Applicants believe that they have shown with numerous examples that $VPAC_2$ receptor specific agonist can be safely and effectively employed to treat muscle mass or function-related diseases and disorders.

iv. The nature of the invention is that it is directed to treating muscle atrophy or inducing muscle hypertrophy in subjects in need thereof. As described in the specification muscle is a tissue that has been very well conserved across different vertebrate species and exhibits similar physiology and function. Further as detailed in the specification, different animal and cell-based models exist to assist in identifying the compounds that regulate muscle specific receptors. Therefore, there is a very high level of predictability in the art as to the outcome of the experiments. Further, muscle biology is a mature field that involves scientists from various different disciplines including, physiology, medicine, molecular biology, chemistry, and so on. Therefore, the level of skill in the field is very high.

v. It is the discovery of the Applicants' that $VPAC_2$ receptors are involved in regulation of muscle mass and function. Applicants have amended the claims to $VPAC_2$ receptor agonists. Applicants believe that with the amended claims the breadth of the claims is commensurate with the invention described in the application. Applicants thus believe that they have satisfied the requirements put forth in *In re WANDS*.

vi. Further as discussed above, the muscle tissue expresses only $VPAC_2$ receptor and neither $VPAC_1$ receptor nor PACAP-type 1 receptor. Therefore, when a $VPAC_2$ receptor-specific agonist is used in the treatment of a subject in need of increased muscle mass or function, the agonist would activate only $VPAC_2$ receptor. Applicants have amended claims 16, and 17 such that only $VPAC_2$ receptor specific agonists are claimed. Thus, the breadth of the claims is commensurate with the teachings presented in the specification. Applicants respectfully submit that amendment to claims 16, and 17, assures that only $VPAC_2$ receptor-specific agonists are used, and that this amendment makes the pending claims allowable.

d. The Office Action also states that Applicants do not show any examples of VPAC receptor antagonists (emphasis added), which induce muscle mass. Applicants have amended the claims to agonists of the $VPAC_2$ receptor. As such, the present amendment overcomes the rejection..

4. Office Action in points 9) and 10) state that claims 16, 17, and 27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 is rejected as indefinite over the recitation of "...a subject in which an increase in muscle mass is desirable..." for not providing a definition of what subjects are classified in this category.

a. Applicants wish to draw attention to page 3, line 15 to page 4, line 2 of the specification. Applicants describe in detail the causes of muscle atrophy that include various diseases and disorders. Applicants also describe how muscle disuse (casting), space travel, and steroid therapies could lead to muscle atrophy. Subjects that are undergoing these therapies or patients suffering from diseases described in the specification are easily identifiable by the medical professional based on their disease status, and are the primary beneficiaries of $VPAC_2$ receptor agonist treatment.

b. Claim 16 and 27 are both allegedly found indefinite for the term "selectively acting." The ordinary meaning of "selective," according to Webster's Collegiate Dictionary, means "highly specific in activity or effect. Extrapolating this ordinary meaning to the biological arts, one skilled in the art will readily appreciate that "selective" means exhibiting a greater affinity for one (receptor) over others (receptors). Depending on the molecular interactions that a compound has with the receptors it may be a mere 10-fold or may be a million-fold selective over a receptor that it does bind poorly. It should be appreciated that most often an agonist is not 100% selective for any particular receptor, given the molecular complexities of agonist-receptor binding, but rather the agonist may exhibit greater selectivity in binding to one receptor as compared to another receptor. In other words, Applicants claim agonists that will bind to $VPAC_2$ preferentially, i.e. with greater affinity, over other receptors like $VPAC_1$ or PACAP-type 1 receptor. For example, Gourlet et al (*Peptides* (1997) 18(3), 403-8), showed that RO 25-1553 exhibits IC_{50} of about 1 nM for $VPAC_2$ receptor, but about 100 nM for $VPAC_1$ receptor and greater than 1 μM for PACAP-type 1 receptor.

5. Office Action in point 12) states that Claim 15 is rejected under 35 U.S.C. §102(b) as being anticipated by Gourlet et al (WO 98/02453). Again, Applicants have canceled Claim 15 and as such, any rejection to the claim is rendered moot.

6. Claims 16, 17, and 27 are also rejected under 35 U.S.C. §102(b) as being anticipated by Vittone et al (*Metabolism* (1997) 46, 89-96). Vittone et al. teach improved muscle function in elderly men (who suffer from the decrease in muscle mass and strength due to age-related decrease in growth hormone, GH, and insulin-like growth factor-I, IGF-I) after administration of single nightly injections of GHRH.

   a. Applicants point out that GHRH is a peptide hormone secreted by hypothalamus that acts on pituitary somatotroph cells to stimulate their proliferation during development and to regulate their ability to produce and secrete growth hormone (GH) (Iguchi et al., J. Biol. Chem. 274, 12108-12114, included in Suppl. IDS). GHRH binds specifically to its receptor GHRH-R that is mainly expressed in anterior pituitary and hypothalamus and is regulated by pituitary-specific transcription factor Pit-1. Thus, the effects seen in the muscle tissue is not the result of GHRH binding to $VPAC_2$ receptor. Vittone fails to teach GHRH as binding to $VPAC_2$ receptor much less as an agonist. Thus, the effects observed

by Vittone et al. in their experiments cannot be due to binding of GHRH to $VPAC_2$ receptor.

b. Further, Applicants have amended the claims to include only $VPAC_2$-specific receptor agonists. In view of the foregoing, Applicants submit that the rejection in view of Vittone et al. is traversed.

Conclusion

In light of the above remarks, it is requested that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, and 102(b). Early and favorable action in the case is respectfully requested.

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. In view of the foregoing, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein, and allowance of Claims 16, and 17.

Respectfully submitted,
Isfort et al.

By Naishadh N. Desai
Agent for Applicant(s)
Registration No. 50,630
(513) 622-0087

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Customer No. 27752

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